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New Novartis medicine Adakveo® (crizanlizumab) approved by FDA to reduce frequency of pain crises in individuals living with sickle cell disease

- *Sickle cell pain crises are unpredictable, severe events associated with life-threatening complications*[1]
- *Adakveo reduced the annual rate of sickle cell pain crises by 45% compared to placebo (1.63 vs 2.98) and the annual rate of days hospitalized (4 vs 6.87) in a 52-week study*[2]
- *Approximately 100,000 people in the United States, most of whom are of African descent, have sickle cell disease*[3]
- *Approval comes approximately two months ahead of FDA's priority review action date, allowing Adakveo to be available to patients more quickly*

Basel, November 15, 2019 – Novartis announced today that the US Food and Drug Administration (FDA) approved Adakveo® (crizanlizumab), previously known as SEG101, to reduce the frequency of vaso-occlusive crises (VOCs), or pain crises, in adult and pediatric patients aged 16 years and older with sickle cell disease.[4] Adakveo represents the first FDA-approved medicine in sickle cell disease that binds to P-selectin –a cell adhesion protein that plays a central role in the multicellular interactions that can lead to vaso-occlusion.[5,6] The medicine is expected to be available to patients in the coming weeks.

The FDA's decision to approve Adakveo 5 mg/kg is based on results of the 52-week, randomized, placebo-controlled SUSTAIN trial, which showed that Adakveo significantly lowered the median annual rate of VOCs to 1.63 vs 2.98 compared to placebo (*P*=.010), which is equivalent to a 45% reduction. Reductions in the frequency of VOCs were observed among patients regardless of sickle cell disease genotype and/or hydroxyurea use.[2,4]

"We know this drug can decrease the frequency of sickle cell pain crises in a significant and clinically meaningful way," said Kenneth Ataga, MD, Director, Center for Sickle Cell Disease, University of Tennessee Health Science Center at Memphis, and Principal Investigator of the SUSTAIN trial. "The approval of crizanlizumab is an important advancement for people living with this very difficult condition."

Additional results from the SUSTAIN study include:[4]

- A decrease in the median annual rate of days hospitalized to 4 vs 6.87 days when compared with placebo (a 42% reduction)
- Thirty-six percent of patients treated with Adakveo did not experience a VOC, compared to 17% of placebo-treated patients
- The median time to first VOC was 4.1 for Adakveo vs 1.4 months for placebo

The most common adverse reactions (incidence > 10%) were nausea (18%), arthralgia (18%), back pain (15%) and pyrexia (11%).[4]

"The approval of Adakveo marks a new era in the treatment of sickle cell disease, a genetic condition that places an extraordinary burden of unpredictable pain crises on patients and

their families," said Susanne Schaffert, PhD, President, Novartis Oncology. "The stories we have heard from patients about their sickle cell pain crises are devastating. We are pleased to help reimagine medicine together with the sickle cell community and offer new hope for fewer VOCs."

Considered the clinical hallmark of the disease, sickle cell pain crises are triggered, in part, by multicellular interactions that form clusters of cells, which can block or reduce the blood flow to organs.[1,7] Sickle cell pain crises can be frequent and sudden, and are associated with an increased risk of life-threatening complications.[1] They also are the main reason why individuals living with sickle cell disease go to the emergency room and are admitted to the hospital.[7]

"Patients with sickle cell disease often face unique challenges, and have long suffered silently through unimaginable pain crises," said Beverley Francis-Gibson, President and CEO of the Sickle Cell Disease Association of America. "We are excited to have a new medicine that may help many of the thousands of people living with sickle cell disease by reducing the frequency of these potentially dangerous and painful episodes."

About Sickle Cell Disease
Sickle cell disease is a complex and debilitating, genetic blood disorder that goes beyond sickle-shaped red blood cells. The disease is associated with chronic inflammation, causing higher levels of cell adhesion proteins, including P-selectin, which make both the blood vessels and certain blood cells stickier and prone to multicellular interactions, or clusters, in the bloodstream. This environment can lead to the acute episodes of pain known as sickle cell pain crises, or VOCs, as well as life-threatening complications.[1,7,8] VOCs are the main reason why individuals living with sickle cell disease seek medical care in hospitals,[7] leading to approximately 200,000 ER visits in the US every year.[9,10]

Approximately 100,000 people in the US have sickle cell disease.[3] People of African ancestry make up 90% of the population with sickle cell disease in the US. However, sickle cell disease is also prevalent among people of Hispanic, South Asian, Southern European, and Middle Eastern ancestry. Sickle cell disease occurs in about 1 in 365 and 1 in 16,300 African-American and Hispanic-American births, respectively.[3]

About Adakveo
Adakveo® (crizanlizumab) – previously known as SEG101 – is indicated to reduce the frequency of VOCs, or pain crises, in adults and pediatric patients aged 16 years and older with sickle cell disease. It is the first and only targeted biologic that works by binding to P-selectin, a cell adhesion protein that plays a central role in the multicellular interactions that can lead to vaso-occlusion in sickle cell disease.

By binding to P-selectin on the surface of the activated endothelium and platelets, Adakveo blocks interactions between endothelial cells, platelets, red blood cells, and leukocytes.[4]

About SUSTAIN
SUSTAIN is a randomized, multicenter, placebo-controlled, double-blind study. A total of 198 patients with any genotype of sickle cell disease (HbSS, HbSC, HbS/beta^0-thalassemia, HbS/beta$^+$-thalassemia, and others) and a history of 2-10 VOCs in the previous 12 months were eligible for inclusion. Patients were randomized 1:1:1 to Adakveo 5 mg/kg (N = 67), Adakveo 2.5 mg/kg (N = 66), or placebo (N = 65) administered over a period of 30 minutes by intravenous infusion on Week 0, Week 2, and every 4 weeks thereafter, for a treatment duration of 52 weeks.

The primary efficacy outcome was the annual rate of VOCs leading to a healthcare visit. A VOC leading to a healthcare visit was defined as an acute episode of pain with no cause other than a vaso-occlusive event that required a medical facility visit and treatment with oral or parenteral opioids, or parenteral NSAIDs. Acute chest syndrome, hepatic sequestration,

splenic sequestration, and priapism (requiring a visit to a medical facility) were also considered VOCs. Key secondary and other efficacy endpoints include annual rate of days hospitalized, time to first VOC leading to healthcare visit, and number of patients that did not experience a VOC.

Patient Access and Support
Novartis is committed to helping ensure that our medicines are accessible to as many patients as possible. With the approval of Adakveo in the United States, we now offer resources and support to address a range of needs. Adakveo Support at PANO (Patient Assistance Now Oncology) is a support center staffed by insurance specialists and case managers who can help eligible patients start and stay on treatment. Dedicated support specialists are available to help direct callers to services that best fit their needs. Patients or providers can call 800-282-7630 or visit Patients.NovartisOncology.com or HCP.Novartis.com/Access to learn more about eligibility and to enroll.

Novartis Commitment to Sickle Cell Disease in Africa
Sickle cell is a global disease and is most widespread in sub-Saharan Africa. Unfortunately, we can see a clear disparity when comparing Africa with other parts of the world, where sickle cell is often managed as a chronic disease. Building on years of engagement in Africa, working to reduce the impact of malaria and other conditions, Novartis is taking steps to help address the needs of sickle cell patients as well, beginning in Ghana. Our partnership with the Ghana Ministry of Health, the Ghana Health Service, and the Sickle Cell Foundation of Ghana aims to improve the diagnosis and treatment of people with sickle cell disease through a comprehensive approach to screening and diagnosis, treatment and disease management, training and education, and elevating basic and clinical research and scientific capabilities. These activities include facilitating access to high-quality hydroxyurea and other basic medicines to enhance the standard of care.

To date, Novartis has delivered more than 20,000 hydroxyurea treatments to Ghana, with plans to deliver a total of 60,000 treatments by the end of the year. In addition, Novartis is developing a child-friendly formulation of hydroxyurea and is committed to implementing two clinical trials with crizanlizumab in Ghana and Kenya – an important step to bringing this innovative medicine to patients. Crizanlizumab trials in Africa are expected to start in 2020.

Indication
Adakveo® (crizanlizumab-tmca) is used in people 16 years of age and older, who have sickle cell disease, to help reduce how often certain episodes of pain (crises) happen. It is not known if Adakveo is safe and effective in children under 16 years of age.

Important Safety Information
Adakveo may cause serious side effects, including infusion reactions. Infusion reactions may happen within 24 hours of receiving an infusion of Adakveo. Patients should tell their health care provider right away if they get any of the following signs and symptoms of an infusion reaction such as fever, chills or shivering, nausea, vomiting, tiredness, dizziness, sweating, hives, itching, or shortness of breath or wheezing. Health care providers may monitor their patients for signs and symptoms of infusion reactions.

Adakveo may interfere with automated platelet counts (platelet clumping). Patients should tell their health care provider that they are receiving Adakveo before having any blood tests. Health care providers should run blood samples as soon as possible or use tubes containing citrate.

Before receiving Adakveo, patients should tell their health care provider if they are pregnant or plan to become pregnant. It is not known if Adakveo may harm an unborn baby.

The most common side effects (incidence ≥10%) include nausea, back pain, joint pain, and fever.

Please see full Prescribing Information for Adakveo at https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/adakveo.pdf.

Disclaimer

This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as “potential,” “can,” “will,” “plan,” “expect,” “anticipate,” “look forward,” “believe,” “committed,” “investigational,” “pipeline,” “launch,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for the investigational or approved products described in this press release, or regarding potential future revenues from such products. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that the investigational or approved products described in this press release will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that such products will be commercially successful in the future. In particular, our expectations regarding such products could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political and economic conditions; safety, quality or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, and other risks and factors referred to in Novartis AG’s current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis

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